UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

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SUBJECT: **Amitraz.** Human Health Risk Assessment

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The following human health risk assessment for amitraz has been prepared by the Health Effects Division for Phase One of the Tolerance Reassessment Eligibility Decision (TRED) process for amitraz. Occupational risk assessment for amitraz is not addressed in this document. Aggregate (food / drinking water / residential) risk assessment is based on the following memoranda:

Amitraz: Report of the Hazard Identification Assessment Review Committee (P. Hurley memo, 3/17/04)

Amitraz: Toxicology Disciplinary Chapter for the Tolerance Reassessment Eligibility Decision Document (P. Hurley memo, 3/17/04)

Amitraz. Product Chemistry Chapter for the TRED Document (J. Morales memo, 4/30/04)

Amitraz: Residue Chemistry Chapter (J. Morales memo, 4/30/04)

Amitraz: Anticipated Residues, Acute, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (J. Morales memo, 4/30/04)

Amitraz: Drinking Water Assessment for Tolerance Reassessment Eligibility Decision (S. Abel memo, 2/11/04)

Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Evaluation Decision (TRED) Document for Amitraz (R. Travaglini memo, 4/30/04)

Review of Incident Reports (J. Blondell memo, In Preparation)

Amitraz Risk Assessment

1.0 Executive Summary

Amitraz [N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide] is an insecticide/acaricide with registered food/feed uses in the U.S. on cotton, pears, beef and dairy cattle, and hogs. Amitraz is currently registered for use on cotton to control various insects (bollworm larvae and eggs, beet armyworm, whitefly, aphids, and spider mites) as well as on pears for the control of pear psylla and grape mealybug. Amitraz is also used for tick control on dogs as well as mite and lice management on beef cattle, dairy cattle and swine.

Amitraz can be applied via dip or low pressure hand spray for cattle and swine with up to 0.2 lb a.i./50 gallons of water. For the use of Taktic E.C. on beef cattle, dairy cattle and swine, the following application methods are suggested: 1) cattle applied via spraying or by a spray dip machine, 2) swine applied via spraying, and 3) piglets/weaners applied by dipping. However, Taktic E.C. is not to be applied within three days of slaughter for swine, which are not to be treated more than four times per year. All of the established tolerances for meats, meat by-products, eggs and milk will be maintained to support the animal health uses.

In the case of tick and flea collars (Preventic® and Preventic® Plus), application should be made every three months in dogs more than 12 weeks of age.

In a recent letter to the Agency, Bayer Crop Science (BCS) has decided to voluntarily withdraw the registrations of Ovaysn Insecticide/Miticide (EPA Reg. No. 264-625) and Mitac W Insecticide (EPA Reg. No. 264-636). The registrant has also requested to maintain the registration of technical amitraz, to revoke established tolerances for apples, beeswax, cotton (US cotton registration is being volunraily revoked) honey, and pears as well as maintain import tolerances for hops and cottonseed (Amitraz Use Closure Memo, 10/22/03).

Amitraz is a FIFRA List A pesticide assigned to Case No. 0234 and was the subject of a Reregistration Standard Guidance Document dated 10/87. The Residue Chemistry Chapter of the Amitraz Reregistration Standard Update was issued 7/6/90. The Residue Chemistry Chapter for the Amitraz Reregistration Eligibility Decision document (RED) was issued 9/17/93, and the Amitraz RED was signed 03/95.

Hazard Assessment

The toxicology database for Amitraz is incomplete. There are several major data gaps. The available studies are not of the most current quality; however, sufficient data may be gleaned from them for use in an assessment of risk to human health. The toxicity profile for Amitraz cannot be completely characterized for all effects, especially those relating to developmental, reproductive and neurotoxic effects.

Amitraz has a low acute toxicity in a wide number of species, including mice, rats, guinea pigs, rabbits, dogs, baboons and domestic pigs by the either the oral, dermal and/or inhalation routes of exposure. A pharmacotoxic profile suggests that amitraz induces a depression of hypothalmic function with clinical signs of central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. Similar clinical signs are observed via oral, dermal or inhalation routes of exposure. The dog appears to be the most sensitive species and there is no indication of extra sensitivity for either sex. Metabolism studies in humans indicate clinical signs similar to those observed in animals. Decreased body weight is the other major effect following exposure to amitraz and there is no concern for cumulative toxicity (i.e. no increased toxicity with a longer term of exposure).

There is no indication of developmental toxicity in the rat in either of two available studies. Although two rabbit developmental toxicity studies and two reproduction studies in the rat are available, none are acceptable for regulatory purposes due to deficiencies in either the study designs and/or the studies themselves. Multiple species display evidence of neurotoxicity following exposure to Amitraz. Signs of CNS depression were observed in the dog and possibly the rabbit. In the rat, irritability, nervousness and/or excitability were observed.

Amitraz is a carcinogen in mice, inducing significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas in females and lung adenomas in males. It is classified as a Group C, possible human carcinogen with a Q_1* of 2.83×10^{-2}.

Amitraz is not stable in the diet and the current toxicological endpoints for risk assessment are based on a capsule or bolus dose study. In the dietary studies, due to significant degradation, the animals are likely more exposed to the degradation products than to the parent. These degradation products also happen to be significant animal and plant metabolites. Therefore, in the diet, humans are more likely to be exposed to the degradation product than to the parent. The capsule study protects for exposure to the degradates because it has a lower toxicological endpoint than the long term dietary studies. The dermal and inhalation endpoints are also based on the capsule study. Humans are more likely to be exposed to the parent via the dermal and inhalation and non-dietary oral routes associated with livestock and pet uses being maintained by the registrant rather than dietary exposures. Consequently, they will be directly exposed to parent, amitraz, without a chance for significant degradation, the capsule study may be more appropriate as the study of choice for these routes (the dermal and inhalation studies are not acceptable).

FQPA Decision

On February 3, 2004, the Hazard Identification Assessment Review Committee (HIARC) determined that the special FQPA safety factor should be reduced to 1X; however, a 10X database uncertainty factor (UF_{DB}) is required due to an incomplete database (i.e. lack of acceptable rabbit developmental toxicity and two-generation reproduction studies). Despite the lack of acceptable rabbit developmental and rat reproduction studies, there are no residual uncertainties for pre- and/or post-natal toxicity based on the the following considerations:

the results of the two unacceptable rabbit developmental studies, when taken together, show that developmental effects occurred at doses higher than the doses that caused maternal toxicity;

a 10X UF_{DB} is required;

the endpoint of concern (neurotoxicity) for the overall risk assessment is based on the "apparent" sensitive species (dogs),

and the selected toxicological endpoint for the overall risk assessment is approximately 20-fold lower than the lowest developmental NOAEL in the unacceptable rabbit studies and 5-fold lower than the offspring NOAEL in the unacceptable three-generation reproduction study.

Based on the weight of evidence presented, the HIARC is concerned about potential reproductive effects and neurotoxicity in developing fetuses. The HIARC is therefore requiring a combined 2-generation reproduction study in the rat with components assessing for potential developmental and adult neurotoxicity.

The HIARC determined that the 10X UF_{DB} should be applied to dietary (acute and chronic) and non-dietary/residential (incidental oral, dermal and inhalation) risk assessments because the required studies may provide endpoints applicable for risk assessments. Therefore, a total UF of 1000 has been applied to all dietary and residential risk assessments.

Dose Response Assessment

The toxicological endpoints for use in human risk assessment for amitraz were selected from the most sensitive species from the amitraz database. A NOAEL of 0.25 mg/kg/day from a chronic oral (capsule) study in the dog was selected for all endpoints for estimation of risk. The endpoint selected is based on signs of neurotoxicity and CNS depression. This NOAEL is the lowest endpoint in the database, from the most sensitive species, and amitraz toxic effects do not cumulate. Therefore, both the acute population adjusted dose (aPAD) and the chronic population adjusted dose (cPAD) = 0.00025 mg/kg/day. Similarly, the NOAEL of 0.25 mg/kg/day was used to estimate risks for dermal, inhalation, and incidental oral exposure, all durations. The dermal absorption factor is 8% based on a dermal absorption study on an amitraz formulation. The target Margin of Exposure (MOE) for risk assessment is 1000 for all residential exposures via the oral, dermal and inhalation routes. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation) plus an additional 10X database uncertainty factor for lack of acceptable developmental rabbit and rat reproduction studies.

Residue Chemistry

The qualitative nature of the residue in plants and animals is adequately understood based on plant metabolism studies with apples, beans, lemons, citrus, cotton, and pears, and animal metabolism studies with cattle and swine (dermal application) and cattle, goats and hens (oral dosing). The terminal residues of concern for risk assessment and enforcement purposes are amitraz and its metabolites containing the 2,4-dimethylaniline (2,4-DMA) moiety [BTS-27919 (N-(2,4-dimethylphenyl) formamide) and BTS-27271 (N-(2,4-dimethylphenyl)-N-methylmethanimidamide)]; these are the residues which are presently included in the tolerance expression.

Dietary Exposure and Risk Estimates

Refined probabilistic acute, chronic, and cancer dietary risk assessments were conducted using DEEM-FCID™ (Version 1.30) and the Lifeline™ Model (Version 2.0) which uses food consumption data from the United States Department of Agriculture's (USDA's). Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Chronic and acute exposure estimates were based on data from dermal metabolism studies provided by the registrant and percent crop treated provided by BEAD. Conservative assumptions were made in the calculation of anticipated residues used in the dietary assessment.

Acute dietary risks, using Lifeline™ Model, are above HED's level of concern for children 1-2 yrs (186% of aPAD, 0.000465 mg/kg/day) and children 3-5 years old (170% of aPAD, 0.000425 mg/kg/day) at the 99.9th percentile of exposure.

Acute dietary risks, using DEEM-FCID™ , are above HED's level of concern for children 1-2 yrs (140% of aPAD, 0.000349 mg/kg/day) at the 99.9th percentile of exposure.

As noted in this risk assessment, DEEM™ and Lifeline™ provided different predicted exposure at the 99.9th percentiles for the 1 to 2 and 3 to 5 year old subpopulations (both exceeding the aPAD). The assessment accounts for exposure from the three RACs: beef, pork and milk. Milk is the primary RAC that drives exposure at the 99.9th percentile due to the relatively high residues. Lifeline had relatively higher predictions for both the 1 to 2 year old (186% vs 140% aPAD), and 3 to 5 year old subpopulations (170% vs 94% aPAD). The different model predictions can be attributed to two reasons: (1) a limitation regarding the Lifeline software, and (2) modeling differences between DEEM™ and Lifeline™ . A complete explanation of how these factors affect the model predictions will be presented in a subsequent memo. The apparent limitation in Lifeline™ software is the result of several concurrent factors: (i) milk is treated as a food comprised of three RACS (water, non-fat solids, fat), (ii) the percent crop treated is relatively low (0.1%), and (iii) the Lifeline™ Food Residue Translator (FRT) approximates food (milk) residue percentiles based on a fixed number of simulations. The difference in modeling design (frequency of using food diaries and weights applied) also contribute towards the Lifeline™ model providing higher exposure estimates than DEEM™ . This latter effect is independent of the first effect, however, it is also dependent upon the percent crop treated value used for milk.

Given the relatively high anticipated residues for milk (0.03 ppm), a moderate amount of milk consumption may provide exposure exceeding the aPAD. For example, a 20 kg toddler (typical 5 year old), consuming 8 ounces of milk (226 grams = 8 x 28.3 grams/oz), or equivalently, 11.3 grams/kg bwt/day (~226/20), would have dietary exposure of approximately 0.0003 mg ai/kg bwt/day (= 0.03 ppm x 11.3 gm/kg bwt/day x (1/1000)), or 135% of the aPAD (=0.00025). The average milk consumption for 1-4 year olds is approximately 337 gm/day, with 75% of toddlers (1to5 year olds) consuming 11 grams/kg bwt/day or more of dairy products. Even though the other two commodities (beef, pork) provide relatively low exposure, milk continues to provide exposure at the 99.9th percentile even with the low percent crop treated due to the application of residues to the three milk components (water, fat, non-fat solids), and the relatively high percent of toddlers that consume milk.

Estimated chronic dietary risk is below HED's level of concern for all populations (<1% of cPAD). Results of the Lifeline™ analysis are fully consistent with DEEM-FCID™ results. The estimated exposure of the general U.S. population to amitraz is <0.000001 mg/kg/day for both dietary risk assessment models. Applying the Q_1* of 2.83 x 10^{-2} $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of 2.8 x 10^{-8}. Therefore, estimated cancer dietary risk is below HED's level of concern.

Surface and Drinking Water Exposure Assessment

SRRD contacted the amitraz registrant and received the following information regarding the use of amitraz as animal dips/sprays. HED is awaiting written verification of this information. The registrant indicated that of the product sold in the US, 25-30% is used on swine operations in NC and the Midwest. They also said that it is almost never used outdoors; the bulk of the treatments are indoors directly to the animal with 10-20% of the applied spray running off the animal to inert (indoor) surfaces. EFED modeled amitraz use on swine based on communications from the registrant regarding animal dips/sprays and assumed that 30% of the product sold in the US was used in such a manner that it was available for runoff in one watershed in NC. There is significant uncertainty in this assessment approach due to the lack of concrete data on use within a watershed, the vulnerability of the application site to runoff, the lack of information on the amount of product applied to a hog that would be available for washoff with the first rainfall or subsequent events, whether the material available for washoff would be amitraz *per se* or one of its degradation products because of its known instability, the proximity of a surface water source to the site of application that would be within reasonable proximity to a drinking water utility, and the possibility that common drinking water treatment processes may affect the stability of any remaining parent amitraz.

The following EECs were generated for use in risk assessment:

Surface water EEC: Typical Estimate: Peak Concentration = 0.1 ppb; Annual Average Concentration = 0.0006 ppb
Groundwater EEC: Typical = 0.000009 ppb

Residential Exposure

Homeowners can be exposed to amitraz via pet collars used on dogs. To assess these potential exposures, toxicological endpoints were selected for short- and intermediate-term dermal, inhalation, and incidental oral exposures; no chronic exposure scenarios are thought to exist for amitraz. In addition, amitraz is classified as a Group C possible human carcinogen and it has a Q_1*of 2.83 x 10^{-2}. The target MOE for residential risk estimates is 1000.

HED considers this residential risk assessment to be based on high-end estimates of exposure generated from screening-level procedures outlined in the *SOPs for Residential Exposure Assessment* (U.S. EPA, 1997, 1999). As such, the risk estimates associated with pet collars are conservative, largely driven by default assumptions and uncertainties in the toxicity database.

Although HED considers the residential handler scenario as having some potential exposure, the most significant exposure of concern is for post-application scenarios as these exposures are of longer duration and may be significant for children. Therefore this document primarily focuses on residential post-application exposures only, and does not address residential handlers. As such, risks were estimated for post-application dermal exposures of adults, and dermal and incidental oral exposures of children for non-cancer effects, and cancer effects from dermal exposures of adults, only.

All post-application scenarios resulted in MOEs which exceed HED's level of concern. Post-application dermal exposure estimates for toddlers indicate MOEs of 22. Incidental oral post-application exposure to toddlers from amitraz (via hand to mouth), from such activities as contacting the dog has an MOE of 65. For adults, dermal post-application exposure estimates for amitraz via such an activity of the hugging the dog indicate MOEs of 35. Post-application cancer risk estimates for adults range from 2.8 x 10^{-5} to 5.6 x 10^{-5}, and exceed HED's level of concern. The 8% dermal absorption factor may be considered conservative given the duration of the study (5 days) compared to the likely dermal exposure of up to 24 hours.

Aggregate Risk Estimates

Acute aggregate risk estimates will not be conducted since the dietary acute risk exceed HEDs level of concern. Short- and Intermediate-Term and cancer aggregate risk estimates will not be conducted since the post application residential exposure scenarios exceed HED's level of concern.

Chronic aggregate risk estimates associated with exposure to amitraz residues in food and water do not exceed HED's level of concern. Estimates of exposure from food were taken from the dietary exposure model results described above (Section 4.2.3). The chronic risk estimates are below the Agency's level of concern for the general U.S. population and all population subgroups.

For considering exposure to residues of amitraz in drinking water, HED has calculated chronic Drinking Water Levels of Comparison (DWLOCs). These values are the maximum concentration of a chemical that can occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled EECs provided by

the EFED (see Section 4.3). DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed HED's level of concern. HED calculated DWLOCs for the following populations: general U.S. population (DWLOC = 9 ppb); females (DWLOC = 8 ppb); infants and children (DWLOC = 2.5 ppb). The chronic DWLOCs for the general U.S. population and all of the representative population subgroups modeled by Lifeline™ are greater than both the surface water and ground water chronic EECs (Surface water EEC:Typical Estimate: Annual Average Concentration = 0.0006 ppb; and Groundwater EEC: Typical = 0.000009 ppb). Therefore, chronic aggregate risk estimates associated with exposure to amitraz residues in food and water do not exceed HED's level of concern.

Incident Reports

Animal incident reports for currently registered amitraz products from 1992 through 2003 were reviewed. In general, there have been few reports of amitraz toxicity in recent years.

The most notable incidents were reports of dogs pulling a tick collar off another dog and ingesting the collar. This has resulted in serious toxicity including bradycardia and depression, resulting in emergency veterinary care. Yohimbine is a specific antidote for amitraz toxicity in dogs.

There were fewer reports for toxicity in dogs while wearing tick collars, including weakness, ataxia, vomiting, or seizures. These reports were unverified.

There were 3 reports of abortions or stillbirths in pigs from 1992 - 1996. These reports were unverified. There were several reports of misuse of cattle/pig formulation on horses or dogs resulting in death.

A review of human incident data is pending and is not available at this time.

Data Gaps

Refer to Section 4.2 for details of tolerance reassessment. Refer to Section 7.0 of this document for specific data gaps.

2.0 Physical/Chemical Properties Characterization

The PC Code and nomenclature of amitraz are listed below in Table 1. The physicochemical properties of amitraz are listed in Tables 2 and 3. The chemical names and structures of amitraz residues of concern are presented in Table 1.

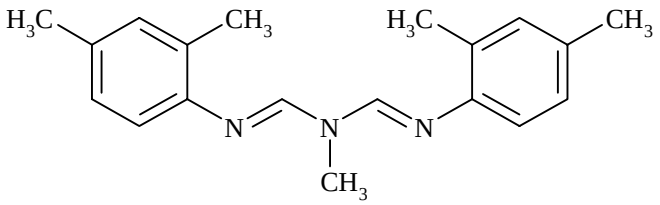
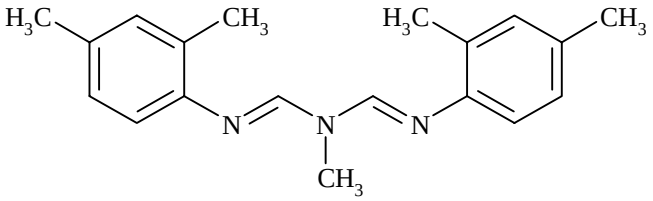
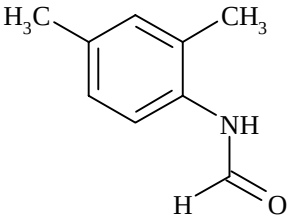
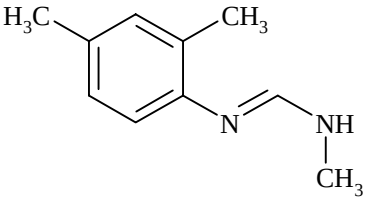
Table 1. Amitraz Nomenclature	
Chemical structure	
Common name	Amitraz
Molecular Formula	$C_{19}H_{23}N_3$
Molecular Weight	293.42
IUPAC name	N-methylbis(2,4-xylyliminomethyl)amine
CAS name	N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide
CAS #	33089-61-1
PC Code	106201
Current Food/Feed Site Registration	Cotton, pear, beef and dairy cattle, hog, goats, horses, sheep

Table 2. Physicochemical Properties of Amitraz.		
Parameter	**Value**	**Reference**
Melting point/range	86-87 °C	Amitraz RED, 03/95
pH of 1% aqueous suspension	N/A (low solubility; decomposes in water)	Amitraz RED, 03/95
Density or specific gravity	1.128 g/mL at 20 °C	Amitraz RED, 03/95
Water solubility	<1 ppm at 20-25 °C	Amitraz RED, 03/95
Solvent solubility	At 20-25 °C xylene 66.6 g/100 mL acetone 50.0 g/100 mL methanol 2.38 g/100 mL	Amitraz RED, 03/95
Vapor pressure	3.4×10^{-4} mm Hg at 25 °C	Amitraz RED, 03/95
Octanol/water partition coefficient (K_{ow})	3.0×10^{5} at 25 °C (pH 5.8)	CBRS No. 3975, 7/21/88, H. Fonouni.

Amitraz is soluble in xylene, acetone, and methanol and insoluble in water. It has a low to moderate vapor pressure and exposure to the gaseous state should be negligible.

Table 3. Chemical Names and Structures of Amitraz and its Residues of Concern.		
Company Name	Chemical Name	Structure
Amitraz	N'-[2,4-dimethylphenyl]-N-[[(2,4-dimethylphenyl)imino] methyl]]-N-methyl-methanimidamide	
BTS-27919	N-(2,4-dimethylphenyl) formamide	
BTS-27271	N-(2,4-dimethylphenyl)-N-methylmethanimidamide	

3.0 Hazard Characterization

3.1 Hazard Profile

General Toxicity Profile

The toxicology database for Amitraz is incomplete. There are several major data gaps. The available studies are not of the most current quality; however, sufficient data may be gleaned from them for use in an assessment of risk to human health. The toxicity profile for Amitraz cannot be completely characterized for all effects, especially those relating to developmental, reproductive and neurotoxic effects.

Acute Toxicity: Amitraz has a low acute toxicity in a wide number of species. The Toxicity Categories reflect low toxicity (Categories II-IV; the II was due to the fact that it was not tested at sufficiently high doses to provide for a higher Category than II). It has been tested in mice, rats, guinea pigs, rabbits, dogs, baboons and domestic pigs by the oral, dermal and inhalation routes of exposure. The Registration Standard (TXR 005633), states that a pharmacotoxic profile suggests a depression of hypothalmic function. Clinical signs of toxicity include central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. These signs varied in severity depending upon the species. The dog appears to be the most sensitive species, with the baboon approximately 2.5 times less sensitive, followed by

the rat and guinea pig (5 times less sensitive). The mouse appears to be the least sensitive (15 times less sensitive). Metabolism studies in humans indicate clinical signs similar to those observed in animals. These signs were reported within 90 to 160 minutes after ingestion and included sedation, dry mouth, disorientation, bradycardia, hypertension and hypothermia persisting up to 12 hours after dosing..

Table 4. Acute Toxicity Data on AMITRAZ Technical

Guideline No./ Study Type	MRID No.	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	00041539	LD_{50}: 531 mg/kg (M) 515 mg/kg (F)	III
870.1200 Acute dermal toxicity	00040862	LD_{50}: > 200 mg/kg	II
870.1300 Acute inhalation toxicity	00029963	LC_{50}: 2.4 mg/L	III
870.2400 Acute eye irritation	00040861	Non-irritating	IV
870.2500 Acute dermal irritation	00040862	Non-irritating	IV
870.2600 Skin sensitization	00029965	Not a sensitizer under conditions of study	N/A

Target Tissues and Species/Sex Sensitivity: Clinical signs of neurotoxicity and decreased body weights appear to be the major targets for amitraz. A comparison of the subchronic and chronic studies indicates that there does not appear to be any issues of cumulative toxicity (i.e. no increased toxicity with a longer term of exposure). The dog is the most sensitive species, although the clinical signs appear early in the chronic study and do not reappear. Similar clinical signs are observed when amitraz is administered via all three routes of exposure: oral, dermal and inhalation. There does not appear to be any extra sensitivity in any one sex.

Developmental/Reproductive Effects: There is no indication of developmental toxicity in the rat in either of two available studies (one unacceptable study and an acceptable repeat study). Two studies are available in the rabbit; however, neither are acceptable due to deficiencies in either the study designs and/or the studies themselves. In the first rabbit study, at a dose level where decreased body weight gains and abortions were observed in the does, decreased litter size, decreased implantations, increased postimplantation loss, abortions and decreased mean fetal body weight had been observed. However, the study needed to be repeated because there were too few litters available for analysis, limited data available in the report and an unclear method of dosing. No developmental toxicity was observed in the second rabbit study; however this study is not acceptable due to too few available litters in the two treated groups and pre-existing maternal respiratory infections. In addition, this study was not tested at as high a dose as in the first study. In the repeat study, an apparent increase in early resorptions and percent postimplantation loss was

seen at the highest dose tested; however, these increases were due to the fact that three does at this dose totally resorbed their litters (88% of the early resorptions were found in the three does which displayed total litter resorptions). It might be possible that developmental toxicity could be observed at a higher dose if a new study were conducted. In summary, there is no evidence (quantitative or qualitative) of increased susceptibility following pre-natal exposure to rats. However, evidence for susceptibility following pre-natal exposure to rabbits could not be ascertained due to deficiencies in either the study designs and/or study reports.

Two reproduction studies are available, a 1-generation and a 3-generation study. In the 1-generation reproduction study, at the same LOAEL, the parents exhibit a mean decrease in body weight gain whereas the pups exhibit a lower mean litter size at birth and on lactation day 4. In the 3-generation reproduction study, the parents exhibit a mean decrease in body weight gain during the F0 premating period at the LOAEL. At the parental NOAEL, the pups exhibit decreased survival and mean litter size during lactation. Unfortunately, neither study is unacceptable for regulatory purposes. In the 1-generation study, the animals are not tested over at least two generations, only limited information were provided and the purity of the test compound was not available. In the 3-generation reproduction study, again, limited data were provided, mating was not 1 male to 1 female, no data on reproductive organs were provided, litter data only provided for a few time points, and histopathology data were not provided. In summary, evidence for susceptibility following pre and/or postnatal exposure to rats could not be ascertained due to many deficiencies in study designs and/or study reports.

Neurotoxicity: Multiple species display evidence of neurotoxicity following exposure to Amitraz. In both the subchronic and chronic oral studies in dogs, signs of CNS depression were observed and a decrease in pulse rate and hypothermia were noted in the subchronic study. In both the subchronic and chronic oral studies and in the 21-day inhalation study in the rat, irritability, nervousness and/or excitability were observed. In the rabbit developmental toxicity study, clinical signs that were considered to be related to treatment included langor and polypnea. Sedation was also observed in rabbits in the repeated dose dermal study.

Carcinogenicity: In rats, there is no indication of potential carcinogenicity for amitraz; however, in female mice amitraz induces significant dose-related positive trends in hepatocellular adenomas, carcinomas and in combined adenomas/carcinomas. Females also had a significant increase in the pair-wise comparison of controls and the highest dose group in hepatocellular adenomas, carcinomas and in combined adenomas and/or carcinomas. Male mice had a significant dose-related positive trend in lung adenomas. In addition, males had a significant increase in the pair-wise comparison of controls and the highest dose group in lung adenomas. Amitraz is classified as a Group C, possible human carcinogen. The Q_1* has been calculated to be 2.83×10^{-2} in human equivalents using the 3/4's scaling factor, reflecting the 1994 Agency policy.

Mutagenicity: Amitraz has not been shown to induce gene mutations in either bacterial or mammalian cells, is not clastogenic in an *in vitro* study, does not induce unscheduled DNA synthesis in mammalian cells, and does not induce cell transformations in C3H/10T1/2 cells derived from mouse embyro fibroblasts under the conditions in which the studies were conducted.

Metabolism: Metabolism studies have been conducted in the mouse, rat, cat, dog, baboon and man. The major metabolites of amitraz include N-(2,4-dimethylphenyl)-N-methylformamidine; 2,4-dimethylformanilide; 2,4-dimethylaniline; 4-amino-3-methylbenzoic acid; 4-formamido-3-methyl benzoic acid; 4-acetamido-3-methyl benzoic acid; and N,N-bis-2,4-dimethylphenylformamidine. 2,4-dimethylaniline is included in the tolerance expression along with the parent.

Toxicological Significance of Effects: The clinical signs of neurotoxicity (i.e. CNS depression or irritability depending upon species) occur across species, sexes and routes of administration. These clinical signs do not appear to be cumulative after multiple doses. In the dog, they appear to be transient. Insufficient data are available as to whether or not irreversible effects may occur.

Table 5. Toxicity Profile of AMITRAZ Technical

Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity rats	NOAEL = 3 mg/kg/day LOAEL = 12 mg/kg/day based on irritability, excitability and reduced overall body weight gain. No individual animal data for clinical signs and gross necropsy.
870.3150 90-Day oral toxicity in dogs	NOAEL = 0.25 mg/kg/day LOAEL = 1.0 mg/kg/day based on CNS depression, decrease in pulse rate, increase in glucose in urine, hypothermia, neutrophilia of bone marrow, increased liver weights and increased extent of liver lesions. Too few animals.
870.3200 21/28-Day dermal toxicity rabbits	NOAEL = Cannot be determined LOAEL = 50 mg/kg/day based on clinical signs (sedation) and a decrease in food consumption in males. Too few animals, concurrent infections, lack of information on the substance tested and limited histopathology.
870.3465 90-Day inhalation toxicity rats	NOAEL = 0.01 mg/L/day LOAEL = 0.1 mg/L/day (nominal) based on clinical signs of toxicity (irritation and neurological signs) and decreases in body weight and body weight gain. Limited individual animal data; analytical exposure concentrations not measured; purity of test material not reported and reporting incomplete in terms of the study protocol and environmental conditions.
870.3700a Prenatal developmental in rats	Maternal NOAEL = 3 mg/kg/day LOAEL = 12 mg/kg/day based on decreases in body weight gain. Developmental NOAEL = 12 mg/kg/day LOAEL = > 12 mg/kg/day [HDT]. Very limited data, dosage period was from gestation days 8-20.
870.3700a Prenatal developmental in rats	Maternal NOAEL = 7.5 mg/kg/day LOAEL = 15.0 mg/kg/day based on decreases in body weight and body weight gain. Developmental NOAEL = 30 mg/kg/day LOAEL = > 30 mg/kg/day [HDT].

Guideline No./ Study Type	Results
870.3700b Prenatal developmental in rabbits	Maternal NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on decrease in body weight gain and abortions Developmental NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased litter size, decreased implantations, increased postimplantation loss, abortions and decreased mean fetal body weight. Too few litters, limited data, unclear method of dosing.
870.3700b Prenatal developmental in rabbits	Maternal NOAEL = not established LOAEL = 3.0 mg/kg/day based on clinical signs. Developmental NOAEL = 12 mg/kg/day LOAEL = > 12 mg/kg/day (HDT). Too few litters in two treated groups and pre-existing maternal respiratory infections.
870.3800 Reproduction and fertility effects (1-generation) rats	Parental/Systemic NOAEL = 3 mg/kg/day LOAEL = 12 mg/kg/day based on decreased body weight gain. Reproductive NOAEL = 12 mg/kg/day LOAEL > 12 mg/kg/day (HDT). Offspring NOAEL = 3 mg/kg/day LOAEL = 12 mg/kg/day based on lower mean litter size at birth and on lactation day 4.
870.3800 Reproduction and fertility effects (3-generations) rats	Parental/Systemic NOAEL = 4.36/5.09 (M/F) mg/kg/day LOAEL = 16.41/20.05 (M/F) mg/kg/day based on decreased body weight gain during the F0 premating period.. Reproductive NOAEL = 16.41/20.05 (M/F) mg/kg/day LOAEL > 16.41/20.05 (M/F) mg/kg/day (HDT). Offspring NOAEL = 1.29/1.58 (M/F) mg/kg/day LOAEL = 4.36/5.09 (M/F) mg/kg/day based on decreased survival and mean litter size during lactation. Limited data provided, mating was not 1 male to 1 female, no data on reproductive organs provided, litter data only provided for a few time points, and histopathology data not provided.
870.4100b Chronic toxicity dogs	NOAEL = 0.25 mg/kg/day LOAEL = 1.0 mg/kg/day based on CNS depression during first two days of dosing.

Guideline No./ Study Type	Results
870.4300 Chronic Toxicity/ Carcinogenicity rats	NOAEL = 2.5/0.97 (M/F) mg/kg/day LOAEL = 10.18/3.13 (M/F) mg/kg/day based on clinical signs (M and F) and decreased body weight gain (M). No evidence of carcinogenicity.
870.4300 Carcinogenicity mice	NOAEL = < 2.31/2.63 (M/F) mg/kg/day LOAEL = 2.31/2.63 (M/F) mg/kg/day based on dose-related incidence of hyperplastic nodules, liver foci, stomach hyperkeratosis and spleen hematopoiesis. Evidence of carcinogenicity: hepatocellular adenomas, carcinomas and combined; and lung adenomas, probably at dose levels above MTD.
Reverse Gene Mutation in *Salmonella typhimurium* 870.5100	Negative up to 10 mg/plate, with and without metabolic activation.
Forward Gene Mutation in mouse lymphoma cells 870.5300	Negative at 0.06-20 g/ml with and without metabolic activation. HDT is highest non-cytotoxic dose.
In Vitro Cytogenetics (Human Lymphocytes) 870.5375	Negative up to cytotoxic and/or insoluble concentrations.
UDS Assay (Human Embryonic Lung Fibroblast) 870.5550	Negative up to cytotoxic concentrations, with and without metabolic activation.
Cell Transformation (no guideline #)	Negative up to cytotoxic concentrations, with and without metabolic activation.
870.7485 Metabolism and pharmacokinetics rats	No sex differences in proportion of various metabolites recovered in 24-hour urine samples. Metabolic process saturated at the 100 mg/kg level. No unchanged parent material found in the urine. Major metabolites: N-(2,4-dimethylphenyl)-N-methyl formamidine, 4-formamido-3-methyl benzoic acid, 4-acetamido-3-methyl benzoic acid and a polar fraction. The polar fraction was labile to acid hydrolysis, yielding conjugates of 4-amino-3-methylbenzoic acid, N-(2,4-dimethylphenyl)-N-methyl formamidine, 4-formamido-3-methyl benzoic acid and 4-acetamido-3-methyl benzoic acid.

Guideline No./ Study Type	Results
870.7485 Metabolism and pharmacokinetics rats	Peak levels of amitraz reached in urine within 8 hours: 78% of the dose in the urine and 9% in the feces by 98 hours. Peak levels of metabolite BTS 27271 reached in urine within 24 hours: 89% of the dose in the urine and 4% in the feces by 96 hours. Highest residues of amitraz and BTS 27271 reported in the liver. Blood residue levels were 17.9 ppb for amitraz and not detectable for BTS 27271. Kidney residue levels were comparable with 18.0 and 24 ppb for amitraz and BTS 27271, respectively. Degradation products of amitraz and its metabolite, BTS 27271 were similar.
870.7600 Dermal penetration rats	The mean percent of dose absorbed: treatment site (2.98% at 24 hours, 1.41% at 120 hours); total absorbed (3.69% at 24 hours, 6.56% at 120 hours); total (6.67% at 24 hours, 7.79% at 120 hours).

3.2 FQPA Considerations

There is no evidence (quantitative or qualitative) of increased susceptibility following pre-natal exposure to rats. However, evidence for susceptibility following pre-natal exposure to rabbits (devlopmental) or following pre and/or postnatal exposure to rats (2-generation reproduction) could not be ascertained due to many deficiencies in study designs and/or study reports. There is a concern for neurotoxicity resulting from exposure to Amitraz. No neurotoxicity studies have been conducted. Evidence of neurotoxicity following exposure to Amitraz is indicated in multiple studies across species and across routes of administration, which include signs of CNS depression in the dog; irritability, nervousness and/or excitability in the rat and langor and polypnea in the rabbit.

The toxicological database for Amitraz is inadequate for assessment of risk to infants and children. Significant data gaps exist, which include an acceptable developmental rabbit study and a multi-generation reproduction study. There is also concern for neurotoxicity and developmental neurotoxicity. No studies are available which access potential neurotoxicity.

There are no concerns for residual uncertainty for pre-natal toxicity in the available developmental toxicity study in rats.

Despite the lack of acceptable rabbit developmental and rat reproduction studies, the HIARC determined that there are no residual uncertainties for pre- and/or post-natal toxicity based on the following considerations:

- Although susceptibility could not be ascertained in rabbits, the results of the two unacceptable studies show that developmental effects occurred at doses higher than the doses that caused maternal toxicity.

- A 10X database uncertainty factor (UF_{DB}) is required due to an incomplete database (i.e. lack of acceptable rabbit developmental toxicity and two-generation reproduction studies).

- At present, the endpoint of concern (neurotoxicity) for the overall risk assessment is based on the "apparent" sensitive species (dogs).

- The dose (0.25 mg/kg/day) selected for the overall risk assessments is approximately 20-fold lower than the lowest developmental NOAEL in the unacceptable rabbit studies and 5-fold lower than the offspring NOAEL in the unacceptable three-generation reproduction study.

Based on the above data, no special FQPA safety factor (i.e. 1X) is required since there are no residual uncertainties for pre-natal toxicity as discussed above. In addition, the drinking water, and residential exposure assessments were conducted using screening-level models and procedures, assumptions and default values that result in high-end estimates that do not underestimate risk. Amitraz metabolites were included in the dietary assessment. Even though the dietary assessment used percent-crop-treated data and anticipated residues (ARs) these values represent high-end residues from feeding studies and do not underestimate dietary exposure and risk..

The HIARC concluded that there is concern for developmental neurotoxicity resulting from exposure to Amitraz based on the indications of clinical signs of neurotoxicity across species, sexes and routes of administration. Based on the weight of evidence presented, the HIARC is requiring a combined 2-generation reproduction study in the rat with components assessing for potential developmental and adult neurotoxicity. The HIARC recommended that the study design for the required two-generation reproduction study should be MODIFIED to include the following:

- Due to the concern for the lack of stability of the test material in the diet, treatment should be via oral (gavage) administration.

- The potential for neurotoxicity in the developing fetuses should be evaluated according to the OPPTS Guideline §870.6300.

- The potential for neurotoxicity in adults should be evaluated according to the OPPTS Guideline §870.6200.

The HIARC determined that the 10X UF_{DB} should be applied to dietary (acute and chronic) and non-dietary (incidental oral, dermal and inhalation) risk assessments because the required studies may provide endpoints applicable for risk assessments.

3.3 Dose-Response Assessment

Discussion of Toxicological Database for Risk Assessment Purposes: The toxicology database for Amitraz is incomplete. There are major data gaps, especially in the studies important for a complete assessment under FQPA. The toxicity profile for Amitraz cannot be completely characterized for all effects, especially those relating to developmental, reproductive and neurotoxic effects.

All of the toxicological endpoints for risk assessment are based on the chronic dog study. This study had a NOAEL of 0.25 mg/kg/day based on clinical signs of neurotoxicity (CNS depression) during the first two days of dosing at the LOAEL of 1.0 mg/kg/day. These clinical signs were observed three hours after administration of a single dose. This toxicological endpoint is supported by similar clinical signs observed in humans following an acute exposure (TXR No. 011110).

Acute Dietary Exposure: The endpoint from the dog study is considered to be appropriate for acute dietary exposure for the general population, including infants and children because it is based on clinical signs of neurotoxicity (CNS depression) which were observed three hours after administration of a single dose.

Chronic Dietary Exposure: Although effects were observed early on in the dog study and were not observed later in the study, this study is appropriate for a chronic dietary endpoint because the dogs were exposed to the test material for 2 years. Additionally, the dose (0.25 mg/kg/day) would address the concerns for systemic effects seen in mice (liver, spleen and stomach lesions) and rats (clinical signs and decrease in body weight gain), following long term oral administration at higher doses.

Incidental Oral Exposure: All Durations (1 - 30 days and 1- 6 Months): The endpoint from the chronic dog study is considered to be appropriate for the population of concern (infants and children). This dose/endpoint is appropriate for both short- and intermediate-term exposure because the effects were observed early in the study (i.e. first two days of dosing), dogs are the most sensitive species and it would address the concern for effects seen via the oral route in other species.

Dermal Exposure: All Durations (1 - 30 days, 1- 6 Months and > 6 Months): The HIARC noted that a 21-day dermal toxicity study in rabbits is available and shows CNS depression at the lowest dose tested, 50 mg/kg/day; a NOAEL was not established. The Committee determined that this study is not suitable for use in risk assessment due to many deficiencies with the conduct of the study. The deficiencies noted were testing of too few animals (4/sex/dose), concurrent infections, lack of test article characterization and limited histopathological evaluation of the required tissues. Therefore, an oral NOAEL from the chronic dog study was selected for dermal risk assessments. Although the endpoint of concern (CNS depression) was seen after a few exposures, it is appropriate for all time periods (i.e., short-, intermediate- and long-term) since the effects were seen in the most sensitive species (dogs) and the selected dose (0.25 mg/kg/day) would address the concerns of systemic toxicity seen in mice and rats following oral administration. Additionally, the use of an 8% dermal absorption value with the 0.25 mg/kg/day oral dose yields a dermal equivalent

dose of 3.1 mg/kg/day (0.25 ÷ 0.08) which is comparable to an extrapolated NOAEL of 5.0 mg/kg/day (50.0 ÷ 10 UF for use of a LOAEL) from the 21-day dermal toxicity study.

Inhalation Exposure: All Durations (1 - 30 days, 1- 6 Months and > 6 Months): The HIARC noted that a 21-day inhalation toxicity study in rats is available with a NOAEL of 0.42 mg/kg/day and a LOAEL of 4.2 mg/kg/day. These values are based on the conversion of nominal values and therefore, are considered to be gross estimates of the actual values. The Committee determined that this study is not suitable for risk assessments due to many deficiencies with the conduct of the study. There were limited individual animal data, analytical exposure concentrations were not measured and the study reports were incomplete in terms of study protocol and environmental conditions. Therefore, an oral NOAEL from the chronic dog study was selected for inhalation risk assessments. Although the endpoint of concern (CNS depression) was seen after a few exposures, it is appropriate for all time periods (i.e., short-, intermediate- and long-term) since the effects were seen in the most sensitive species (dogs) and the selected dose (0.25 mg/kg/day) would address the concerns of systemic toxicity seen in mice and rats following oral administration.

Carcinogenicity: As stated previously, amitraz has been classified as a Group C, possible human carcinogen based on an increased incidence of hepatocellular adenomas, carcinomas and combined adenomas/carcinomas in female mice. Male mice had a significant dose-related positive trend in lung adenomas. In addition, males had a significant increase in the pair-wise comparison of controls and the highest dose group in lung adenomas. The Q_1* has been calculated to be 2.83 x 10^{-2} in human equivalents using the 3/4's scaling factor, reflecting the 1994 Agency policy.

Toxicology Endpoint Selection Table

Summary of Toxicological Dose and Endpoints for Amitraz

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children)	NOAEL = 0.25 mg/kg/day UF = 1000 **Acute RfD** = 0.00025 mg/kg/day	FQPA SF = 1 aPAD = acute RfD / FQPA SF = 0.00025 mg/kg/day	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Chronic Dietary (All populations)	NOAEL= 0.25 mg/kg/day UF = 1000 **Chronic RfD** = 0.00025 mg/kg/day	FQPA SF = 1 **cPAD** = chronic RfD / FQPA SF = 0.00025 mg/kg/day	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short- and Intermediate - Term Incidental Oral (1-30 days and 1-6 months)	NOAEL= 0.25 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** = NA	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Dermal (All Durations)	Oral NOAEL= 0.25 mg/kg/day (dermal absorption rate 8%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Inhalation (All Durations)	Oral NOAEL= 0.25 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Cancer (oral, dermal, inhalation)	$Q_1^* = 2.83 \times 10^{-2}$ Group: C		Combined hepatocellular adenomas and carcinomas in female mice.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and

resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, amitraz may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Exposure Assessment and Characterization

4.1 Summary of Registered Uses

Amitraz [N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide] is an insecticide/acaricide with registered food/feed uses in the U.S. on cotton, pears, beef and dairy cattle, and hogs. Amitraz is currently registered for use on cotton to control various insects (bollworm larvae and eggs, beet armyworm, whitefly, aphids, and spider mites) as well as on pears for the control of pear psylla and grape mealybug. Amitraz can be applied by airblast and concentrate spray (pears) with up to 3.0 lb a.i./acre applied during dormancy and throughout the growing season excluding prebloom applications. It can also be applied via ground boom or aircraft (cotton) with up to 1.0 lb a.i./acre during the growing season with a maximum of eight applications per year. Current formulations include: wettable powder, emulsifiable concentrate, and soluble concentrate/liquid. In addition, an import tolerance has been established to support amitraz use on hops to be imported into the U.S. Amitraz products with food/feed uses are registered in the U.S. to Bayer CropScience (BCS) LP and Intervet, Inc. under the trade names Ovasyn®, Mitac®, and Taktic®. Currently, the 1.5 lb/gal soluble concentrate (SC), 50% wettable powder (WP), and 12.5% emulsifiable concentrate (EC) formulations are registered for use on food/feed sites. The SC formulation is registered for use on cotton, and the WP formulation is registered for use on pears. The EC formulation is registered for use on cattle and swine as dermal treatments.

Amitraz is also used for tick control on dogs as well as mite and lice management on beef cattle, dairy cattle and swine. In the case of tick and flea collars (Preventic® and Preventic® Plus), application should be made every three months in dogs more than 12 weeks of age. Additionally, amitraz can be applied via dip or low pressure hand spray for cattle and swine with up to 0.2 lb a.i./50 gallons of water. For the use of Taktic E.C. on beef cattle, dairy cattle and swine, the following application methods are suggestedl: 1) cattle applied via spraying or by a spray dip machine, 2) swine applied via spraying, and 3) piglets/weaners applied by dipping. However, Taktic E.C. is not to be applied within three days of slaughter for swine, which are not to be treated more than four times per year. All of the established tolerances for meats, meat by-products, and milk will be maintained to support the animal health uses.

In a recent letter to the Agency, BCS has decided to voluntarily withdraw the registrations of Ovaysn Insecticide/Miticide (EPA Reg. No. 264-625) and Mitac W Insecticide (EPA Reg. No. 264-636). The registrant has also requested to maintain the registration of technical amitraz, to revoke established tolerances for apples, beeswax, cotton, honey, and pears as well as maintain import tolerances for hops and cottonseed (Amitraz Use Closure Memo, 10/22/03).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Tolerances for residues of amitraz in/on plant and animal commodities are expressed in terms of the combined residues of "amitraz (N'-[2,4-dimethylphenyl]-N-[[(2,4-dimethylphenyl)imino]methyl]]-N-methylmethanimidamide) and its metabolites N-(2,4-dimethylphenyl)-N-methyl formamide and N-(2,4-dimethylphenyl)-N-methylmethanimidamide," both calculated as the parent compound [40 CFR §180.287].

Tolerances have been established under 40 CFR §180.287 for the combined residues of amitraz and its two metabolites, N-(2,4-dimethylphenyl) formamide and N-(2,4-dimethylphenyl)-N-methylmethanimidamide, both calculated as the parent compound in/on cotton, undelinted seed, at 1 ppm, honey at 1 ppm, honeycomb at 6 ppm, dried hop cones at 60 ppm, and pear at 3 ppm, and in animal commodities at levels ranging from 0.01 to 0.3 ppm.

The HED Chem SAC (3/31/04 meeting) has recommended that the current tolerance expression for amitraz needs to be changed by removing the reference to specific metabolites. The tolerance expression should specify that the terminal residues of concern for enforcement purposes are amitraz and its metabolites containing the 2,4-dimethylaniline moiety.

A summary of the amitraz tolerance reassessments and recommended modifications in commodity definitions is presented in Table 6.

Nature of the Residue - Plants and Livestock

The qualitative nature of the residue in plants and animals is adequately understood based on plant metabolism studies with apples, beans, lemons, citrus, cotton, and pears, and animal metabolism studies with cattle and swine (dermal application) and cattle, goats and hens (oral dosing).

Residue analytical methods - Plants and Animals

Adequate tolerance enforcement methods are listed in PAM Volume II for the determination of amitraz residues of concern in plant and animal commodities.

Enforcement methods: There are two adequate methods listed in FDA's Pesticide Analytical Manual (PAM Vol. II) for purposes of data collection and enforcement of tolerances for residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety. Methods I (designed for animal tissues and milk) and II (designed for plant commodities) are both GLC methods with electron capture detection (ECD), and involve conversion of residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety to 2,4-DMA using acid and base hydrolysis, respectively. The detection limits of the methods are 0.01 ppm for milk and 0.05 ppm for plant commodities and animal tissues.

The enforcement methods have not been radiovalidated; however, the data collection method for plant commodities (similar to Method II) was successfully radiovalidated using samples from the pear metabolism study. Because the extraction procedure is extensive (hydrolysis with acid at reflux), the Agency will not require radiovalidation data for the enforcement method for animal commodities.

Data collection methods: A GC/ECD method was used for the determination of amitraz residues of concern in hops. This method differs from the enforcement method for plant commodities in that residues are extracted/hydrolyzed using acid and then basified to convert to 2,4-dimethylaniline; 2,4-dimethylaniline residues are then distilled into hexane. In Method II of PAM Vol. II, base hydrolysis is used to extract residues and convert them to 2,4-dimethylaniline; these residues are then partitioned into isooctane. HED has recommended that this method be forwarded to FDA for publication in PAM Vol. II as Method A.

Amitraz residues of concern in animal commodities were determined using a GC/ECD method similar to the method used for hops.

Storage Stability

Adequate data are available to support the existing crop field trial and feeding studies.

Storage stability studies have been conducted using fortified samples of citrus fruits, cow tissues and milk, and cottonseed. Residues of amitraz are stable in cottonseed for 13.5 months of frozen storage, and residues of BTS-27271 and BTS-27919 are stable in/on citrus fruits stored frozen (-20 C) for up to 18 months; these data may be translated to hops. Residues of amitraz, BTS-27271, and BTS-27919 are stable in cow tissues and milk stored frozen (-20 C) for up to 12-15 months, and in hog muscle and fat stored frozen (-15 C) for at least 12 months. The storage intervals and conditions from the magnitude of the residue studies in plants and animals are adequately supported by storage stability data.

Crop Field Trials

Since the registrant is requesting cancellation of all U.S. registrations on crops used as foods/feeds, residue data on crops are not relevant to this risk assessment.

Processed Commodities

The 9/93 RED Chapter concluded that the reregistration data requirements pertaining to magnitude of the residues in processed food/feed were fulfilled. Adequate cotton processing studies indicate that amitraz residues of concern do not concentrate in the hull meal, crude oil, refined oil, and soapstock processed from cottonseed following application at exaggerated rates.

Rotational Crops

The 9/93 RED Chapter concluded that additional data were required to upgrade the available confined rotational crop study to allow a conclusion to be made regarding the magnitude of residues in rotational crops. These data were considered confirmatory for the purposes of reregistration. The RED Chapter also noted that field rotational crop studies had been reviewed by EFED and deemed acceptable.

Since the 9/93 RED Chapter, the available field rotational crop studies, originally reviewed by EFED, have been evaluated by HED. It was concluded that the limited field rotational crop studies were adequate and that additional data were no longer needed to upgrade the confined rotational crop study. The available data support rotational crop restrictions of 44 days for root and leafy vegetables and 60 days for small grains and other crops, which are the established rotational crop restrictions for use of amitraz on cotton. Rotational crop tolerances are not needed.

The registrants have stated that they intend to cancel use of amitraz on cotton, the only annual crop with registered uses. Therefore, no data pertaining to confined and field accumulation in rotational crops are required.

Codex Harmonization

Several maximum residue limits (MRLs) for amitraz have been established by Codex in various commodities. The Codex MRLs are currently expressed as the sum of amitraz and N-(2,4-dimethylphenyl)-N'-methylformamidine calculated as N-(2,4-dimethylphenyl)-N'-methylformamidine.

The Codex tolerance expression is somewhat different from the U.S. tolerance expression. The Codex expression is the sum of amitraz plus metabolite BTS-27271, calculated as BTS-27271. The U.S. expression is the sum of amitraz and its metabolites BTS-27271 and BTS-27919, both calculated as the parent compound. The enforcement methods for amitraz tolerances in the U.S. (Methods I and II of PAM Vol. II) consists of hydrolysis of all metabolites containing the 2,4-DMA moiety to 2,4-DMA and determination using gas chromatography with electron capture detection. The enforcement method under the Codex system involves treatment of the RAC with acidic methanol to convert the parent compound to metabolite BTS-27271, followed by extraction, cleanup, and determination of BTS-27271 using gas liquid chromatography with flame ionization detection. Presently, compatibility between the Codex MRL and U.S. tolerance cannot be achieved due to the differences between the tolerance definitions and analytical enforcement methods.

The current U.S. tolerances and Codex MRLs are identical in magnitude for cattle and pig meat. However, the reassessed tolerances in the U.S. are lower than Codex MRLs with the exception of milk which are the same. There are several Codex MRLs for which there are no U.S. tolerances.

Tolerance Reassessment

The HED Chem SAC (3/31/04 meeting) has recommended that the current tolerance expression for amitraz needs to be changed by removing the reference to specific metabolites. The tolerance expression should specify that the terminal residues of concern for enforcement purposes are amitraz and its metabolites containing the 2,4-dimethylaniline moiety.

Adequate residue data have been submitted to reassess the established tolerances for the following commodities: cattle, fat; cattle, meat byproducts; cattle, meat; hog, fat; hog, kidney; hog, liver; hog, meat byproducts; hog, meat; hop, dried cones; milk; and milk, fat. The available data indicate that the established tolerances for cattle meat byproducts, hog liver and kidney, and milk fat may be reduced. The tolerances for cattle fat, hog fat, hog meat byproducts, hog meat, hop dried cones, and milk are reassessed at the same level. We note that for dried hops, because the percent dry matter was not known for all samples submitted in support of the tolerance petition, HED recommended a tolerance level higher than the maximum observed residues to account for the potential that the samples had dry matter contents different from the expected value of approximately 85%. A U.S. registration/tolerance for hops was never established.

Because the tolerance for dried hops under 40 CFR §180.287 is an import tolerance, the tolerance listing should be amended with a footnote stating "No U.S. registrations as of [date of FR notice]". The registrant has indicated that they would like to keep the cotton tolerance as an import tolerance. HED notes that there is a Codex MRL for cottonseed. If a Codex MRL has been established, the NAFTA countries may conduct a more limited review of the residue chemistry data under certain conditions. The NAFTA countries are more likely to adopt MRLs similar to Codex MRL levels if MRLs for the pesticide are already established on other commodities with a contemporary robust database. Standard data and review requirements would be applied where exposure and/or risk to any subpopulation from the pesticide is high. An EPA-specific detailed description of how the U.S. may consider Codex MRLs as they relate to data requirements can be found in Unit VIII of the U.S. Import Tolerances Guidance document (65 FR 35069). The registrant needs to submit a formal request to the Agency for establishment of the cottonseed tolerance as an import tolerance, and information about the use pattern in foreign countries, and residue data from those countries to support the request.

All registered uses of amitraz in beehives have been cancelled, and the registrants intend to cancel use of amitraz on cotton and pears in the U.S. Therefore, the established U.S. (Section 3) tolerances for the following commodities should be revoked: cotton, undelinted seed; honey; honeycomb; and pear. In addition, because there will no longer be any dietary exposure of livestock to amitraz, the established tolerances for the following animal commodities should be revoked: egg; goat, fat; goat, meat byproducts; goat, meat; poultry fat/meat; poultry meat byproducts; sheep, fat; sheep, meat byproducts; and sheep, meat. Tolerances for horse commodities were previously revoked (67FR 49606, 7/31/02).

Table 6. Tolerance Reassessment Summary for Amitraz.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.287:			

Table 6. Tolerance Reassessment Summary for Amitraz.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Cattle, fat	0.1	0.04	
Cattle, meat byproducts	0.3	0.2	
Cattle, meat	0.05	0.02	
Cotton, undelinted seed	1	1	The registrant intends to cancel use of amitraz on cotton in the US and to retain the tolerance as an import tolerance for cottonseed. The following footnote should be added to the tolerance listing for cottonseed: "No U.S. registrations as of [date of FR notice]."
Egg	0.01	Revoke	When use of amitraz on cotton is cancelled, there will be no need for tolerances for poultry commodities.
Goat, fat	0	Revoke	When use of amitraz on cotton is cancelled, there will be no need for tolerances for goat commodities.
Goat, meat byproducts	0	Revoke	
Goat, meat	0	Revoke	
Hog, fat	0.1	0.1	
Hog, kidney	0.2	0.1	
Hog, liver	0.2	0.1	
Hog, meat byproducts	0.3	0.3	*Hog, meat byproducts, except kidney and liver*
Hog, meat	0.05	0.05	
Honey	1	Revoke	There are no longer any registered uses of amitraz in beehives.
Honeycomb	6	Revoke	
Hop, dried cones	60	60	The registrant intends to retain the import tolerance on hops. The following footnote should be added to the tolerance listing for dried hop cones: "No U.S. registrations as of [date of FR notice]."
Milk	0.03	0.03	
Milk, fat	0.3	0.2	
Pear	3	Revoke	The registrant intends to cancel use of amitraz on pears.
Poultry fat/meat	0.01	Revoke	When use of amitraz on cotton is cancelled, there will be no need for tolerances for poultry commodities.
Poultry meat byproducts	0.05	Revoke	
Sheep, fat	0	Revoke	When use of amitraz on cotton is cancelled, there will be no need for tolerances for sheep commodities.
Sheep, meat byproducts	0	Revoke	

Table 6. Tolerance Reassessment Summary for Amitraz.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Sheep, meat	0	Revoke	

Currently, there are registered direct animal treatments of amitraz to beef and dairy cattle and hogs. The only registered amitraz use with associated livestock feed items is cotton, which the registrants do not intend to support. The 9/93 RED Chapter indicated that it is highly unlikely that beef cattle would be exposed to amitraz via consumption of treated commodities; dairy cattle in milksheds in which cottonseed is readily available may be exposed to amitraz both dermally and in the diet. Residues of amitraz in meat, fat, and meat byproducts are likely to result from dermal application only, while amitraz residues in milk may be the result of dermal application and/or consumption of the treated feed commodity. Since cottonseed registration in the U.S. will not be supported by the registrant, residues in milk will only result from dermal application.

Refined probabilistic acute, chronic, and cancer dietary risk assessments were conducted using DEEM-FCID™ (Version 1.30) and the Lifeline™ Model (Version 2.0) which uses food consumption data from the United States Department of Agriculture's (USDA's). Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Chronic and acute exposure estimates were based on data from dermal metabolism studies provided by the registrant and percent crop treated provided by BEAD. Conservative assumptions were made in the calculation of anticipated residues used in the dietary assessment.

Currently, amitraz may be applied twice to beef and dairy cattle as a 0.05% ai spray, with a 7-day retreatment interval and no pre-slaughter interval (PSI). Hogs may be treated four times per year with a solution containing 0.36 lb ai/100 gal, or 0.05%. A 3-day PSI has been established. Although an acceptable dairy cattle feeding study has been submitted, the only magnitude of the residue data relevant to the current use pattern are dermal application data. Cotton seed imported as a feed item for poultry is insignificant.

Data have been submitted reflecting total amitraz residues (residues of amitraz and its metabolites convertible to 2,4-dimethylaniline) in cattle matrices following dermal treatment. Cattle were treated twice with either a 0.05% or 0.15% ai spray solution with a 7-day retreatment interval and then sacrificed at pre-slaughter intervals of 1, 3, 7, and 14 days. The results of this study are presented below.

Pre-slaughter Interval (days)	% ai in Spray	Maximum Total Amitraz Residues (ppm) in Cattle			
		Muscle	Liver	Kidney	Fat
1	0.05 (2 applications)	0.02	0.09	0.13	0.04
3		0.01	0.08	0.08	0.07
7		<0.01	0.04	0.02	0.02
14		<0.01	0.02	0.01	0.01
1	0.15 (2 applications)	0.05	0.24	0.31	0.09
3		0.02	0.15	0.21	0.09
7		<0.01	0.07	0.07	0.04
14		<0.01	0.03	0.01	0.02

In addition, in a study in which lactating dairy cattle were treated with two sprays containing 0.025%, 0.05%, or 0.10% amitraz, with a 10-day retreatment interval, total amitraz residues in milk were 0.003-0.013 ppm, 0.006-0.025 ppm, and 0.012-0.038 ppm, respectively. Residues were found to concentrate 5x in butterfat.

Data have been submitted reflecting total amitraz residues in hog matrices following dermal treatment. Hogs were sprayed to runoff with a solution containing 0.1% amitraz. Two applications were made seven days apart, and the hogs were slaughtered one day following the second treatment. Maximum combined residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety were <0.05 ppm in muscle, 0.06 ppm in fat, 0.05 ppm in liver, and 0.07 ppm in kidney.

A second hog study reflecting dermal application was conducted in which hogs were treated with a solution of 2 oz (0.05% amitraz) or 4 oz (0.10 % amitraz) of product (Taktic E.C.) in 3 gal of water. A second application was made seven days after the first, and hogs were slaughtered 1, 3, 7, and 14 days following treatment. Maximum combined residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety were 0.006 ppm in muscle, 0.017 ppm in fat, 0.038 ppm in liver, and 0.039 ppm in kidney from hogs slaughtered 3 days following treatments at 2 oz product/3 gal (approximately 1x).

A hog skin processing study has also been submitted. The results of this study indicated that residues in hog skin and puffed rind exceeded 0.2 ppm and that a 0.3-ppm tolerance was appropriate for hog meat byproducts.

Based on the above dermal studies, the following residue data were used for chronic, acute, and cancer assessments:

Table 7. Residue Values for Amitraz.		
Commodity	Residue Value Used for the Chronic and Cancer Assessments (ppm)	RDFs Used in the Acute Assessment
Cattle, fat	0.04	CattleFat(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.04
Cattle, meat byproducts	0.2	CattleMbyp(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.2
Cattle, meat	0.02	CattleMeat(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.02
Hog, fat	0.1	PigFat(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.1
Hog, kidney	0.1	Pig Kidney/Liver(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.1
Hog, liver	0.1	Pig Kidney/Liver(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.1
Hog, meat byproducts	0.3	PigMbyp(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.3
Hog, meat	0.05	PigMeat(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.05

Table 7. Residue Values for Amitraz.		
Commodity	Residue Value Used for the Chronic and Cancer Assessments (ppm)	RDFs Used in the Acute Assessment
Milk	0.03	Milk(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.03
Milk, fat	0.2	MilkFat(%CT=0.1) TOTALNZ=1 TOTALZ=999 0.2

For all commodities, a percent livestock treated value of 0.1% was used (communication between BEAD and HED, 2/23/04).

4.2.2 Acute Dietary

The results of the acute dietary exposure analysis at the 95th, 99th, and 99.9th percentiles of exposure are reported in Table 8.

Table 8. Results of Acute Dietary Exposure Analysis Using both DEEM-FCID™ and Lifeline™ Softwares (DEEM-FCID™ results on the line below for purposes of comparison)

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.00025	0.000001	<1	0.000008	3	0.000098	39
		0.000001	<1	0.000020	<1	0.000063	25
All Infants (<1year old)	0.00025	0.000001	<1	0.000008	3	0.000162	65
		0.000001	<1	0.000001	<1	0.000090	36
Children 1-2 years old	0.00025	0.000001	<1	0.000050	20	0.000465	186
		0.000001	<1	0.000007	3	0.000349	140
Children 3-5 years old	0.00025	0.000001	<1	0.000042	17	0.000425	170
		0.000001	<1	0.000006	2	0.000234	94
Children 6-12 years old	0.00025	0.000001	<1	0.000017	7	0.000168	67
		0.000001	<1	0.000004	2	0.000137	55
Youth 13-19 years old	0.00025	0.000001	<1	0.000008	3	0.0000100	40

Table 8. Results of Acute Dietary Exposure Analysis Using both DEEM-FCID™ and Lifeline™ Softwares (DEEM-FCID™ results on the line below for purposes of comparison)							
Population Subgroup	**aPAD (mg/kg/day)**	**95th Percentile**		**99th Percentile**		**99.9th Percentile**	
		Exposure (mg/kg/day)	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**
		0.000001	<1	0.000001	<1	0.000060	24
Adults 20-49 years old	0.00025	0.000001	<1	0.000006	2	0.000062	25
		0.000001	<1	0.000001	<1	0.000044	18
Adults 50+ years old	0.00025	0.000001	<1	0.000006	2	0.000069	28
		0.000001	<1	0.000001	<1	0.000040	16
Females 13-49 years old	0.00025	0.000001	<1	0.000007	3	0.000072	29
		0.000001	<1	0.000001	<1	0.000043	17

Acute dietary risks, using Lifeline™ Model, are above HED's level of concern for children 1-2 yrs (186% of aPAD, 0.000465 mg/kg/day) and children 3-5 years old (170% of aPAD, 0.000425 mg/kg/day) at the 99.9th percentile of exposure.

Acute dietary risks, using DEEM-FCID™ , are above HED's level of concern for children 1-2 yrs (140% of aPAD, 0.000349 mg/kg/day) at the 99.9th percentile of exposure.

As noted in this risk assessment, DEEM™ and Lifeline™ provided different predicted exposure at the 99.9th percentiles for the 1 to 2 and 3 to 5 year old subpopulations (both exceeding the aPAD). The assessment accounts for exposure from the three RACs: meat, pork and milk. Milk is the primary RAC that drives exposure at the 99.9th percentile due to the relatively high residues. Lifeline™ had relatively higher predictions for both the 1 to 2 year old (186% vs 140% aPAD), and 3 to 5 year old subpopulations (170% vs 94% aPAD). The different model predictions can be attributed to two reasons: (1) a limitation regarding the Lifeline™ software, and (2) modeling differences between DEEM™ and Lifeline™ . A complete explanation of how these factors affect the model predictions will be presented in a subsequent memo. The apparent limitation in Lifeline™ software is the result of several concurrent factors: (i) milk is treated as a food comprised of three RACS (water, non-fat solids, fat), (ii) the percent crop treated is relatively low (0.1%), and (iii) the Lifeline™ . Food Residue Translator (FRT) approximates food (milk) residue percentiles based on a fixed number of simulations. The difference in modeling design (frequency of using food diaries and weights applied) also contribute towards the Lifeline™ model providing higher exposure estimates than DEEM™ . This latter effect is independent of the first effect, however, it is also dependent upon the percent crop treated value used for milk.

Given the relatively high anticipated residues for milk (0.03 ppm), a moderate amount of milk consumption may provide exposure exceeding the aPAD. For example, a 20 kg toddler (typical 5 year old), consuming 8 ounces of milk (226 grams = 8 x 28.3 grams/oz), or equivalently, 11.3

grams/kg bwt/day (~226/20), would have dietary exposure of approximately 0.0003 mg ai/kg bwt/day (= 0.03 ppm x 11.3 gm/kg bwt/day x (1/1000)), or 135% of the aPAD (=0.00025). The average milk consumption for 1-4 year olds is approximately 337 gm/day, with 75% of toddlers (1to5 year olds) consuming 11 grams/kg bwt/day or more of dairy products. Even though the other two commodities (beef, pork) provide relatively low exposure, milk continues to provide exposure at the 99.9th percentile even with the low percent crop treated due to the application of residues to the three milk components (water, fat, non-fat solids), and the relatively high percent of toddlers that consume milk.

4.2.3 Chronic and Cancer Dietary

The results of the chronic dietary exposure analysis are reported in the summary table below. Results of the Lifeline™ analysis are fully consistent with DEEM-FCID™ results. Estimated chronic dietary risk is below HED's level of concern for all populations (<1% of cPAD).

The estimated exposure of the general U.S. population to amitraz is <0.000001 mg/kg/day for both dietary risk assessment models. Applying the Q_1* of 2.83 x 10^{-2} $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of 2.8 x 10^{-8}. Therefore, estimated cancer dietary risk is below HED's level of concern. Results are shown in the Table below.

Table 9. Summary of Acute, Chronic, and Cancer Dietary Exposure and Risk Estimates for Amitraz.

Population Subgroup	PAD, mg/kg/day	DEEM-FCID™		Lifeline™	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)					
U.S. Population	0.00025	0.000063	25	0.000098	39
All infants (< 1 yr)	0.00025	0.000090	36	0.000162	65
Children 1-2 yrs	0.00025	0.000349	140	0.000465	186
Children 3-5 yrs	0.00025	0.000234	94	0.000425	170
Children 6-12 yrs	0.00025	0.000137	55	0.000168	67
Youth 13-19 yrs	0.00025	0.000060	24	0.00010	40
Adults 20-49 yrs	0.00025	0.000044	18	0.000063	25
Adults 50+ yrs	0.00025	0.000040	16	0.000069	28
Females 13-49 yrs	0.00025	0.000043	17	0.000073	29
Chronic Dietary Estimates					
U.S. Population	0.00025	0.000001	<1	0.000001	<1
All infants (< 1 yr)	0.00025	0.000001	<1	0.000001	<1
Children 1-2 yrs	0.00025	0.000001	<1	0.000001	<1
Children 3-5 yrs	0.00025	0.000001	<1	0.000001	<1
Children 6-12 yrs	0.00025	0.000001	<1	0.000001	<1
Youth 13-19 yrs	0.00025	0.000001	<1	0.000001	<1

Table 9. Summary of Acute, Chronic, and Cancer Dietary Exposure and Risk Estimates for Amitraz.					
Population Subgroup	PAD, mg/kg/day	DEEM-FCID™		Lifeline™	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Adults 20-49 yrs	0.00025	0.000001	<1	0.000001	<1
Adults 50+ yrs	0.00025	0.000001	<1	0.000001	<1
Females 13-49 yrs	0.00025	0.000001	<1	0.000001	<1
Cancer Dietary Estimate					
U.S. Population	0.028	<0.000001	2.8×10^{-8}	<0.000001	2.8×10^{-8}

4.3 Water Exposure/Risk Pathway

Application information was insufficient to conduct an exposure assessment that could be referenced to a registrant's supported label. Labels were clear only on the maximum number of applications that could be applied to animals or inert surfaces in a year, the intervals between application for controlling certain pests, and the mixing directions. Application quantities were in general terms such as, "apply to animals until runoff". To address the lack of clear application rates per unit area, SRRD contacted the registrant for more information. As a result EFED conducted "what if" scenarios for estimating drinking water exposures. All of these scenarios assumed that the amitraz applied is applied within one watershed. HED and EFED understand that these assumptions may not represent the typical/actual use of amitraz in animal facilities and they likely overestimate actual environmental exposures (EECs). Details of the drinking water assessment can be found in the EFED drinking water memo.

SRRD contacted the amitraz registrant and received the following information regarding the use of amitraz as animal dips/sprays. HED is awaiting written verification of this information. The registrant indicated that of the product sold in the US, 25-30% is used on swine operations in NC and the Midwest. They also said that it is almost never used outdoors; the bulk of the treatments are indoors directly to the animal with 10-20% of the applied spray running off the animal to inert (indoor) surfaces. EFED modeled amitraz use on swine based on communications from the registrant regarding animal dips/sprays and assumed that 30% of the product sold in the US was used in such a manner that it was available for runoff in one watershed in NC. The following EECs were generated for use in risk assessment:

Surface water EEC: Typical Estimate: Peak Concentration = 0.1 ppb; Annual Average Concentration = 0.0006 ppb
Groundwater EEC: Typical = 0.000009 ppb

4.4 Residential Exposure/Risk Pathway

Amitraz is registered as an insecticide/miticide for the control of ticks, mange mites, lice on domestic livestock such as dairy and beef cattle and swine. Amitraz is also registered for use in/on dog collars for the control of fleas and ticks. For the purposes of this Tolerance Reassessment

Eligibility Decision (TRED) document, HED is concerned with use of amitraz on dog collars for the control of fleas and ticks on the dog only. EPA published a Registration Eligibility Document (RED) for amitraz in March, 1995. In the RED, EPA assessed occupational applicator exposure to amitraz for handlers and applicators as well as post-application occupational exposure resulting from agricultural uses registered for amitraz at that time. Residential uses were not assessed for the RED.

A regulatory review of residential exposure to amitraz [N-methylbis(2,4-xylyliminomethyl)amine] was conducted for this TRED because there is potential exposure to non-occupational (residential) handlers (applicators) during handling and application of pet collars which have been impregnated with the active ingredient amitraz to dogs for the prevention of canine ticks and fleas. There is also potential residential post-application exposure to amitraz for the duration of the use of the collar on the dog.

As of the date of this document, pesticide products containing amitraz are intended for both occupational (i.e., cattle dipping) and residential uses (i.e., dog collars). There are two Federally registered dog collar products impregnated with amitraz, manufactured in France for Virbac of Fort Worth, Texas; EPA Reg. Nos. 2382-104 and 2382-170. Each of these collars contain 9.0% amitraz as the active ingredient. EPA Reg. No. 2382-170 also contains 0.5% Pyripoxyfen as an active ingredient and each product label contains the language "For Veterinary Use Only". According to product labeling, the collars kill ticks, fleas and flea eggs on a dog for three months. For the purposes of this assessment, HED used EPA Reg. No. 2382-170* to estimate potential residential exposure to the insecticide amitraz via it's use in impregnated pet collars on domestic dogs for the prevention of fleas and ticks.

According to the labeling associated with this active ingredient, the collars prevent ticks for 3 months, therefore, the collars can be applied 4 times per year. Product labeling specifies only the use of these collars on dogs.

The March 17th, 2004 report of the Hazard Identification Assessment Review Committee (HIARC) for amitraz identified toxicological endpoints of concern for amitraz. All calculations completed in this document are based on the most current toxicity information available for amitraz. For short and intermediate term dermal and inhalation exposures, and incidental exposures a NOAEL of 0.25 mg/kg/day with a LOAEL of 1.0 mg/kg/day, from a chronic oral study based on CNS depression during the first two days of dosing was selected. A dermal absorption factor of 8.0% is applied for dermal exposure for route to route extrapolation.

A Q_1* based upon female rat liver (carcinoma and/or adenoma) tumor rates was generated using mg/kg b.w.$^{\wedge 2/}_{3}$'s/day cross species scaling factor. The revised unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Amitraz based upon female mouse liver combined adenoma and carcinoma tumor rates is 2.83 x 10^{-2} in human equivalents (converted from animals to humans by use of the $^{3}/_{4}$'s scaling factor - Tox_Risk program, Version 5.31, K. Crump, 2000).

The HIARC determined that a Margin Of Exposure (MOE) of 1000, based on an uncertainty factor of 100X for traditional inter and intra species variation and an additional 10X for lack of acceptable developmental and reproductive data is adequate for residential exposures.

One applicator/handler scenario and three post-application scenarios were identified and and considered in this assessment.The scenarios identified and examined in this TRED:

- Adult residential handler (applicator), the person unwraps the collar and places it on the dog - dermal.

- Toddler - dermal (post-application)

- Toddler - incidental oral (post-application)

-Adult - dermal (post-application)

Intermediate-term dermal and oral MOEs were calculated for this assessment. A target MOE of 1000 is considered adequate for intermediate-term residential exposure via dermal and oral routes.

In this TRED, HED also estimated dermal postapplication cancer risks for adults. (Cancer risk estimates < 1×10^{-6} are not of concern.)

4.4.1 Home Uses

4.4.1.1 Handler

Although HED considers the residential handler scenario as having potential exposure risk, the most significant exposure of concern is for post-application scenarios as these exposures are of longer duration and potentially affect more sensitive residents including infants and children. Therefore this document primarily focuses on residential post-application exposures only, and does not address residential handlers.

4.4.2 Postapplication

As stated above, HED considers post-application exposure to residents, including children, to be the primary concern of potential exposure to amitraz via this registered use. Residents (adults and children) can be exposed to amitraz via its use in a dog collar. Once the collar is applied the amitraz residues potentially are spread throughout the surface area of the dog exposing residents to these residues by dermal contact with the treated dog. Therefore, HED assessed residential post-application exposure to amitraz via its presence in the collar on the dog and thereby potentially spreading throughout the fur of the dog. Identifying toddlers as the most sensitive of potentially exposed residential populations, HED conducted post-application, intermediate-term risk assessments for toddlers and adults. For toddlers, one assessment was based on the likely dermal exposure of a toddler contacting (hugging) the dog, and a second assessment based on incidental

oral ingestion through hand-to-mouth actions after contacting (vigorous petting) the dog. An assessment for dermal exposure of adults, based on contacting the dog , was also conducted.

Since the vapor pressure for amitraz = 3.4 x 10^{-4} mm Hg, and as such, is considered low to moderate, HED feels that there is potential inhalation exposure as a certain amount of off-gassing is expected to occur. However, HED did not address post-application inhalation exposures as the dermal exposures exceeded HED's levels of concern and data concerning inhalation exposures via pet collars was not available.

Residential risks attributable to non-dietary ingestion and dermal exposure were assessed for toddlers and adults after contact with treated pets based on the guidance provided in the *SOPs for Residential Exposure Assessment* (U.S. EPA, 1997, 1999)[1], and also *Exposure to Children and Adults to Transferable Chlorpyrifos Residues from Dogs Treated with Flea Control Collars (Boone, J.s. et al. 2001)*[2]. *Boone, J. et al.* also served as a source of surrogate data for transferrable pesticide residues from dog fur. (To this date, HED has received no chemical specific data concerning this use pattern from the amitraz registrant(s).

The dermal contact scenario is based on the use of the transferable residue data normalized by the sampling area and by the amount of active ingredient in the collar (in units of g/cm2/gram ai). A linear relationship between the active ingredient and the residues is assumed. The transferable residues are then extrapolated to the surface area of a "hug" (i.e., 1875 cm2 - toddlers). No data are available to determine the frequency of "hugs". However, the transferability of the residues from the 5 minute vigorous petting routine in the study is a reasonable surrogate for the transferability of a days worth of "hugs" of a dog by a child.

To determine an "area" weighted mean of the residues from the neck with collar, neck without collar, and back of the dog hugged, a simplistic use of proportions (i.e., thirds) of the three monitored areas of the dog was used. That is, residues measured on the neck of the dog with collar, without collar, and the back of the dog from 1 to 168 days after treatment (DAT) were weighted by 1/3 each, summed and averaged. The initial 4 - hour measurement was not included in the time-weighted average (TWA). The surrogate value to be used as the dermal TWA transferable residue of amitraz is 0.29 g/cm2/gram ai (or 0.29 g/cm2/gram ai x 1875 cm2 hug = 540 g/gram ai for toddlers and 0.29 g/cm2/gram ai x 5625 cm2 hug = 1630 g/gram ai for adults). This represents a unit daily exposure for an intermediate to chronic duration.

The traditional estimates of hand-to-mouth exposure are based on estimates of residues on a child's hand, the frequency of which the hand goes in the mouth, and the duration the child is in contact with the treated surface. While duration estimates are available for a child playing outside (e.g., on lawn), no estimates of contact time are available for pets. Therefore, it is recommended for the pet collar scenario that the oral hand-to-mouth route be based on the amount of residue transferred from the neck with the collar (highest of the three areas monitored). The residues available from the 5 minute vigorous petting routine is believed to be a conservative estimate of the amount of residue available for ingestion for a day. It is believed to be a conservative estimate because it represents 7.5 seconds of petting *prior to each of 40 hand-to-mouth events* (i.e., (5 minutes sampling x 60 seconds/minute) / (2 hours per day x 20 hand-to-mouth events per hour)).

The two hour duration is arbitrary, only presented as a point of reference. Furthermore, the biological monitoring data, even though inconclusive for regulatory decisions, do not indicate any dose levels higher than that estimated by the residue method. However, more research is needed in this area of pet collar exposure.

Labels for the impregnated collars state efficacy for three months, therefore, the maximum application to the dog would be four times/year. The net weight of the collar is 42g with 9.0% amitraz yields 3.8 g active ingredient (ai) in the collar (EPA Reg. No. 2382-170*).

A series of assumptions and exposure factors served as the basis for completing intermediate-term homeowner non-cancer, post-application risk assessments. Each assumption is detailed below:

- The average body weight of an adult used in all assessments is 70 kg. For toddler assessments, 15 kg weight was used as directed by SOPs for Residential Exposure Assessment.

- The amount of available pesticide on the dog's fur as a result of wearing the treated collar on a Time Weighted Average (TWA) = 0.29 ug/cm^2 /g ai as a transferable unit of residue.[2]

- In calculating potential post-application dermal exposure for such dog related activities as contacting, HED used the following surface areas (the dermal contact area) of a hug to a dog: toddler = 1875 cm^2; adults = 5625 cm^2.[1]

Thus the equation for Estimated Absorbed Dermal Dose (EADD) exposure postapplication for residents becomes:

EADD = Transferable residue x fraction transferred x application rate x dermal absorption/ body weight.

Thus for toddlers:

- EADD (mg/kg/day) = (0.29 ug/cm^2 /g ai) x 0.001 mg/ug x 1875 cm^2 x (3.8 g ai Amitraz pet collar) x Dermal Absorption(DA*)/ 15 kg.

And, the equation for Estimated Absorbed Dermal Dose (EADD) exposure postapplication for adults becomes:

- EADD (mg/kg/day) = (0.29 ug/cm^2 /g ai) x 0.001 mg/ug x 5625 cm^2 x (3.8 g ai Amitraz pet collar) x Dermal Absorption(DA*)/ 70 kg.

Toddler Hand-to-Mouth exposure from Residential Exposures Assessment SOPs was calculated as follows:

Dose (mg/kg/day) = (Dog's neck with collar of 1.5 ug/cm^2 /gram ai x 3.8 gm ai Amitraz/collar x 0.001mg/ug x 0.5 saliva extraction efficiency x 20 cm^2 palmar surface area of fingers into mouth)*/15 kg body weight.

Where: *Neck with collar of 1.5 μg/cm2/gram ai = (TWA 340 μg neck with collar/88 cm2 child's palm) / 2.54 gram ai in chlorpyrifos test collar. [child's palm surface area is 350 cm2 for both hands; therefore, 175 cm2 represents one hand and 88 cm2 represents the palm of one hand]. Using the child's hand assumes that the sampling area of the dog (258 cm2) would yield the same amount of transferable residue regardless if the hand used to pet the dog was an adult's hand (as monitored in the study) or a smaller hand of a child.

MOE = NOAEL (0.25 mg/kg/day)/Estimated Absorbed Daily Dose (EADD)

*Dermal Absorption = 8.0%.

Table 10. represents the calculated residential MOEs for various activities as related to amitraz treated dog collars.

Table 10. Residential Post-Application Intermediate-Term Risk Estimates

Resident	Dog Related Activity	EADD * (mg/kg/day)	MOE
Toddler	contacting	0.011	22
Toddler	hand to mouth	0.0038	65
Adult	contacting	0.007	35

* EADD = Estimated Absorbed Dermal Dose
MOE = NOAEL (0.25 mg/kg/day)/Estimated Absorbed Dermal Dose

Postapplication Cancer Risks

To assess carcinogenic risk for amitraz exposure through the examined use, HED selected contacting the animal as the most likely or common vector of concern for the potential exposure over the course of a lifetime. HED therefore used the same Estimated Absorbed Dermal Dose (EADD) described above in the non-cancer risk estimates and extrapolated over a 70 year lifetime, using high and low end lifetime expectations for the dog (10 and 20 years) and employing the following assumptions:

- The dog will wear the treated collar throughout it's lifetime (estimated for 10 and 20 years).
- A dog owner will hug his or her dog once a day over the lifetime of the dog.
- As in the case of post-application non-cancer estimates, the Time Weighted Average (TWA) of available pesticide on the dog's fur is constant.

Hence, the equation for carcinogenic risk estimate over a lifetime for the examined use, utilizing Q_1* method becomes:

- LADD (Lifetime Average Daily Dose) = (EADD) x (number hugs/year) x (number of years of pet ownership/ 70 year lifetime).

– Carcinogenic Risk = (LADD) x (Q_1*), where Q_1* = 2.83 x 10E-2 (mg/kg/day E-1) (Memorandum February 11, 2004).

The following table represents the numerical risk estimation for carcinogenic residential handler risk associated with application of pet collars impregnated with amitraz.

Table 11: Residential Post-Application Carcinogenic Risk Assessment Over a Lifetime

Estimated Lifetime of Treated Dog	Estimated Absorbed Daily Dose[a] (mg/kg/day)	Amortization		LADD[b] (mg/kg/day)	Carcinogenic Risk[c] (mg/kg/day)
		# of Days Exposed /Year	Years of lifetime (70 yrs)		
10 years	0.007	365	10/70	0. 001	2.8×10^{-5}
20 years	0.007	365	20/70	0.002	5.6×10^{-5}

a. Estimated Absorbed Daily Dermal Dose is from Table 3.
b. LADD (lifetime average daily dose) = (absorbed dermal dose) x (number of days exposed/ 365days) x (number of years of pet ownership/70 year lifetime)
c. Carcinogenic Risk = (LADD)*(Q_1^*), where the Q_1^*, is 2.83 x 10E-2 $(mg/kg/day)^{-1}$

Risk Characterization and Uncertainties

HED considers this residential risk assessment to be based on high-end estimates of exposure generated from screening-level procedures outlined in the *SOPs for Residential Exposure Assessment* (U.S. EPA, 1997, 1999). As such, the risk estimates associated with pet collars are conservative, largely driven by default assumptions and uncertainties in the toxicity database.

5.0 Aggregate Risk Assessments and Risk Characterizations

Acute aggregate risk estimates will not be conducted since the dietary acute risk exceed HEDs level of concern. Short- and Intermediate-Term and cancer aggregate risk estimates will not be conducted since the post application residential exposure scenarios exceed HED's level of concern.

Chronic aggregate risk estimates associated with exposure to amitraz residues in food and water do not exceed HED's level of concern. Estimates of exposure from food were taken from the dietary exposure model results described above (Section 4.2.3). The chronic risk estimates are below the Agency's level of concern for the general U.S. population and all population subgroups.

For considering exposure to residues of amitraz in drinking water, HED has calculated chronic Drinking Water Levels of Comparison (DWLOCs). These values are the maximum concentration

of a chemical that can occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled EECs provided by the EFED (see Section 4.3). DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed HED's level of concern. HED calculated DWLOCs for the following populations: general U.S. population (DWLOC = 9 ppb); females (DWLOC = 8 ppb); infants and children (DWLOC = 2.5 ppb). The chronic DWLOCs for the general U.S. population and all of the representative population subgroups modeled by Lifeline™ are greater than both the surface water and ground water EECs (Surface water EEC:Typical Estimate: Annual Average Concentration = 0.0006 ppb; and Groundwater EEC: Typical = 0.000009 ppb). Therefore, chronic aggregate risk estimates associated with exposure to amitraz residues in food and water do not exceed HED's level of concern.

6.0 Cumulative

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Amitraz is a member of the formamidine class of pesticides. This class also includes chlordimeform among others. The formamidine, as a group, have been determined to share a common mechanism of toxicity (July 2001 memo from Office Director Marcia Mulkey). However, a cumulative risk assessment has not been performed as part of this review because the Agency is currently examining approaches for completing this type of assessment. EPA's Office of Research and Development is currently investigating the pharmacokinetics and pharmcodynamics of formamidines which will provide a more solid scientific foundation for the cumulative assessment of these pesticides in the future.

7.0 Data Needs/Label Requirements

Toxicology

870.3700: Prenatal developmental toxicity study in rabbits

870.3800: A two-generation reproduction study which should be MODIFIED to include the following:

- Due to the concern for the lack of stability of the test material in the diet, treatment should be via oral (gavage) administration.

- The potential for neurotoxicity in the developing fetuses should be evaluated according to the OPPTS Guideline §870.6300.

- The potential for neurotoxicity in adults should be evaluated according to the OPPTS Guideline §870.6200.

870.3465: HED recommends reserving the requirement for a 28-day inhalation study following the OPPTS Guideline, with cessation of exposure at 28 days.

Rationale for reserving 28-day inhalation toxicity study:

HED is reserving the requirement for a 28-day inhalation study in rats pending future uses of amitraz based on the following rationale. Currently, amitraz is registered for residential use in pet collars and for commercial use as livestock dips and sprays. Exposure via inhalation from pet collars impregnated with amitraz is expected to be less than dermal exposures associated with that use. HED has focused on post-application dermal and incidental oral exposures for the registered residential uses of amitraz. Estimated dermal exposures alone result in risk estimates that exceed levels of concern. Regarding commercial dips and sprays, the occupational risk assessment conducted for the 1995 Reregistration Eligibility Decision (RED) on amitraz, states that because of adequate ventilation in treatment areas inhalation exposure is minimal. The RED included additional personal protective equipment (PPE) to mitigate exposures of workers to amitraz using sprays. In addition, the current NOAEL of 0.25 mg/kg/day from a dog study results in MOEs of 60 - 600 for combined dermal + inhalation exposures for the livestock spray use, i.e., approaching or greater than the target MOE of 100. The 1995 RED indicates that dermal exposures are approximately 10X inhalation exposures.

Although HED cannot waive the inhalation study because amitraz does not meet the criteria of low toxicity via the inhalation route, low vapor pressure, and inhalation MOEs greater than 1000, and the subchronic toxicity database is incomplete, HED does not believe a 28-day inhalation toxicity study is warranted at this time. However, HED reserves the right to require this study pending future uses of amitraz.

Product Chemistry

All pertinent product chemistry data requirements are satisfied for the only registered manufacturing use product, the Bayer CropSciences 97% T, except that data are required concerning the UV/visible absorption of the PAI (OPPTS 830.7050). Provided that the registrant submits the data required in the attached data summary table for the amitraz technical product, and either certifies that the suppliers of beginning materials and the manufacturing process have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, the Agency has no objections to the reregistration of amitraz with respect to product chemistry data requirements.

Residue Chemistry

Provided that the registered uses on cotton and pears are cancelled, there are no residue chemistry deficiencies pertaining to amitraz reregistration. However, the registrant has indicated that they would like to keep the cotton tolerance as an import tolerance. HED notes that there is a Codex

MRL for cottonseed. If a Codex MRL has been established, the NAFTA countries may conduct a more limited review of the residue chemistry data under certain conditions. The NAFTA countries are more likely to adopt MRLs similar to Codex MRL levels if MRLs for the pesticide are already established on other commodities with a contemporary robust database. Standard data and review requirements would be applied where exposure and/or risk to any subpopulation from the pesticide is high. An EPA-specific detailed description of how the U.S. may consider Codex MRLs as they relate to data requirements can be found in Unit VIII of the U.S. Import Tolerances Guidance document (65 FR 35069). The registrant needs to submit a formal request to the Agency for establishment of the cottonseed tolerance as an import tolerance, and information about the use pattern in foreign countries, and residue data from those countries to support the request.

Non-Dietary Exposure

875.2400 Dermal Exposure Study

Non-Guideline Dog Fur Residue Study